Gene Drive Systems: Suitable Solution for Vector Borne Diseases

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Abstract- Gene-drive systems enhance the likelihood of a sequence passing on to future generations and eventually through a local population and ultimately to all connected population of a species. While genetically engineering an organism means that only that specific organism will carry the specific modifications, using gene drive systems ensures that their offspring will carry the same modifications too which will eventually spread throughout the entire population. Gene drive systems are a more efficient way of genetically engineering an entire population or part of a population in a specific region. With the advent of vector-borne diseases, gene drives provide a sustainable solution to the problem. However, it also raises many ethical and logistical concerns Many countries are looking to gene drives to combat vector borne diseases which thus makes it imperative to understand gene drive systems along with its possible consequences and challenges. The aim of this research paper is to explain the process of gene drive systems as a method to combat vector-borne diseases, and to take note of future challenges and consequences.

Index Terms- Genetic engineering, Gene drive systems, Vector borne diseases, CRISPR, Cas9, Insects, Public Healthcare, Outbreaks

1 INTRODUCTION

Vector-borne diseases refer to those diseases that are caused by parasites, bacteria, and viruses that are transmitted by vectors. Every year there are more than 700,00 deaths from diseases such as malaria, dengue, schistosomiasis, human African trypanosomiasis, leishmaniasis, Chagas disease, yellow fever, Japanese encephalitis and onchocerciasis. The impact of these diseases is highest in tropical and subtropical areas, with the poorest populations being disproportionately affected. [1]

Keeping this is mind various methods have been deployed to combat these diseases. However, sustainable solutions have yet to be found. We require large scale sustainable solutions that are long-term and do not have any adverse effects on the local human population and the ecosystem of the area. This is where gene drive systems step in.

Gene drives work by ensuring that a particular genome will be favoured by natural selection, hence ensuring that the desired trait is eventually spread throughout the whole population. Naturally occurring selfish genetic elements increase the odd them being inherited. They can be used to control various diseases by alteration. By changing the traits which are favoured, transmission of insect-borne pathogens can be blocked which will eventually spread through the whole disease. Transmission of insect-borne pathogens can be blocked which will eventually spread through the whole population. The disease can be controlled in this manner. Without a gene drive, these traits would disappear very quickly from the population since they put the organisms at a disadvantage. However, gene drives ensure this the trait spreads throughout the population even if it does not particularly benefit them. The disease can be controlled in this manner.

The advent of RNA- guided Cas9 nuclease has opened up many new ways to engineer organisms and overcome previous problems.

They have enormous potential and if used effectively can block the transmission of these lethal diseases. Large field experiments have been carried out in Brazil and Florida Keys has also agreed to conduct one in 2021. Genetically modified mosquitoes will be released in order to combat dengue and the Zika virus.

2 IMPACT OF VECTOR BORNE DISEASES

Vector borne diseases refer to those diseases which are spread by invertebrate organisms such as mosquitoes. These organisms carry and transmit the pathogens which lead to outbreak of these diseases. Mosquitoes have been noted to spread many deadly diseases and cause many deaths worldwide. Their ability to transmit pathogens leads to millions of deaths every year. Half the world population is at risk due to living in areas where this mosquito species is present. [2]

These diseases include malaria, dengue, schistosomiasis, human African trypanosomiasis, leishmaniosis, Chagas disease, yellow fever, Japanese encephalitis and onchocerciasis. A billion people are affected annually with poorer parts of the population being more susceptible due to lack of access to adequate housing, safe drinking water, and sanitation. [3]

Mosquitoes are one of the most common vectors and are responsible for various diseases. Diseases spread via mosquitoes have killed more people than all the wars in history. [4] Out of all the disease transmitting insects, mosquitoes have been termed as the greatest threat due to

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their extensive population and various diseases they spread. Malaria is an endemic in 91 countries with 500 million cases every year. Dengue has 20 million cases every year with 2500 million people at risk. Lymphatic filariasis (elephantiasis) infects about 120 million people. [5] The economic impact of these diseases is also severe, with both individuals and governments being impacted. The cost of treatment, medicines, prevention is borne by induvial coupled with loss in income since they cannot work. The government is also impacted since they have to bear several costs since they have to carry out public health interventions, purchase of medicine and supplies, maintenance of hospitals and payment of workers. Direct costs of malaria have been estimated to be about US$ 12 billion per year. [6] The cost of lost economic growth has been noted to be many times more than that. However, this is only limited to malaria and not other vector-borne diseases. The total economic impact of vector borne diseases is substantial.

Most vector management techniques today focus on reducing contact with the vectors and preventing the disease. Though they might help in preventing the disease, the disease in itself is not eradicated and will continue to affect others who do not have access to such methods. Modern methods are focused on reducing vector-human contact. [7] Many people cannot afford or do not have access to the various techniques mentioned, which is why disease burden is disproportionately high on poorer people. [8]

3 GENE DRIVE SYSTEMS AS A SUITABLE COMBATANT

An emerging idea to curb the spread of these diseases is to make use of gene drives. With advancements in the field of gene engineering it is possible now to edit the genes of these vectors in such a way that they do not carry these pathogens. If these pathogens are not carried, the disease will not be transmitted. However, these edits only last two generations and do not get carried out to the whole population.

To exemplify this, let us say that the genes of a mosquito are edited in such a way that it does not carry the pathogen. Once this is released into the wild, it reproduces with a wild mosquito (whose genes have not been edited). When they reproduce, statistically, the edits would only be inherited by half the population, since during reproduction there will be a 50% chance that the offspring inherits the same modifications. [9] When that half reproduces, even then only half of their offspring would share the same edits. Hence, as the generations go on, only half of the offspring will inherit the edits while the other half continues to be unimmune to the malarial parasite and transmit the disease. To make an actual impact and reduce the number of diseases, many such mosquitoes would have to be engineered and even then, compared to the total population of the mosquitoes, the disease will continue to run rampant and there will only the be slightest of decrease in the spread of the disease.

Gene drives work by increasing the chances of a trait being inherited by future generations from 50% to 100%. It is a way to distribute a trait throughout the whole population. When the engineered organisms reproduce with wild organisms, all of their offspring will have the modifications and when they reproduce, even their organisms will have the same traits. Eventually, these traits will spread throughout a whole population. [10]

Gene drives have been noted to exist naturally too. In such cases the frequency of the gene increases while being transmitted to the next generations. This unequal transmission gives the gene an edge and leads to a natural gene drive. This is based on transmission radio distortion, in which either of two alleles do not follow the Mendelian law of inheritance and are instead preferentially transmitted to the next generation. [11] They target gametogenesis to ensure that they are over-represented following meiosis, hence ensuring their transmission. These traits get inherited even if they may not be particularly beneficial to the organism.

4 SYNTHETIC GENE DRIVES

Synthetic gene drive systems refer to those which have been created synthetically by scientists and triggered by them. They do not occur naturally and can be altered. One of the earliest concepts of a 'synthetic gene drive' was given by Christopher Curtis. He developed the first mathematical model showing how a naturally occurring desirable gene could spread to fixation in a population. He based it on a gene "to make mosquitoes non-infectible by pathogens." The model showed that enough members of the population would possess the gene in order to ensure that infectability does not strike the mosquito population again.[12]

Technical methods of endonuclease gene drives were mentioned for one of the first times by Austin Burt in a paper in 2003. [13] However, the idea was very difficult to implement of a large scale due to difficulty of engineering homing endonucleases to cut new target sequences. With recent improvements in gene editing technology, using gene drives to combat diseases has become a reality. Past research along with the current technology has given scientists today the ability to alter gene mechanisms in order to make past theoretical proposals a reality.

5 MECHANISM OF SYNTHETIC GENE DRIVES

CRISPR (**C**lustered **R**egularly-**I**nterspaced **S**hort **P**alindromic **R**epeats) are produced

naturally by host bacteria in conjunction with Cas9 (CRISPR associated protein 9) to defend themselves against foreign genetic insertions, which can be done by viruses. It removes viral DNA by targeting repeats associated with viral insertions.

This is used in gene editing by also using a guide RNA. The guide RNA along with CRISPR/Cas9 cuts the DNA of the cell at a sequence that is complimentary to the guide RNA. This gives scientists the ability to remove existing DNA sequences or add new ones, hence 'modifying' the organism.

Synthetic gene drives work by transforming the target organism into a construct that contains the gene for the Cas9 protein, guide RNA complimentary to sequence at intended insertion sit, and the 'cargo' gene controlling the desired trait. This can be referred to as a 'transgene' or a 'gene drive cassette'.[14] Due to the guide RNA the Cas9 protein makes a double stranded cut at the site of the chromosome. Since one part of the chromosome has been cleaved by Cas9, the cell is triggered to copy the entire transgene. This leads to the desired trait being copied on both the chromosomes along with guide RNA and Cas9 protein. If these changes are made in the germ cells, they will be passed on to the next generation and since the entire mechanism has been transferred, the same process will keep occurring in the future generations. These traits will persist even after mating with wild or genetically unmodified organisms which will eventually lead to spread of the trait amongst the entire population.

Standard gene drives aim to cause a population's genotype to change. However, it is important to note that there are also suppression gene drives. Their main aim is population suppression and they spread an element that decreases the number of individuals in the population. The number of organisms reduces or the population might even become extinct due to accumulation of recessive mutations. Another method of using suppression gene drives is ensuring that only male offspring will be produced by cutting X chromosome during male meiosis. The decrease in the number of females will lead to a decline in population or even extinction. [15]

6 IMPACT OF GENE DRIVE ON VECTOR DISEASE ELIMINATION

With the advent of CRISPR/Cas9 technology many models have been developed to predict and study the impact of gene drives on vector diseases. Models for particular regions with a focus on a specific disease have been developed. Scientists in 2015 confirmed the effectiveness and efficiency of gene drive systems. The team initially started with two mosquitoes, both male. After two generations of cross-breeding, the team had over 3,800 third-generation mosquitoes. Out of these third generation mosquitoes, 99.5% expressed genes which made them resistant to malaria. [16]

Due to concerns that wild populations may develop resistance to the gene drive, scientists have been successful in developing suppression gene drive systems that may reduce or make a specific species extinct. There exist over 3000 mosquito species in nature, but by targeting only 3-4 specific species various vector diseases can be eradicated. Such gene drives have been developed and researches at Imperial College, London revealed that their gene drive led to the extinction of a whole population of lab-bred mosquitoes in less than eleven generations. They targeted Anopheles gambiae and altered the genes so that infertile female mosquitoes were created. The gene drive has been deemed to be resistance-proof and the lab conditions were made to mimic that of tropical locations across Sub-Saharan Africa.[17]

7 FIELD TRIALS OF GENE DRIVES

Gene drive systems raise various ethical, legal, and social concerns which need to be addressed in order for proper and safe implementation of this technology. The US National Academies of Sciences, Engineering, and Medicine (NASEM) convened an independent committee to provide an objective assessment about gene drives. The committee's report, "Gene drives on the horizon: Advancing science, navigating uncertainty, and aligning research with public values," concluded that while there was a lack of support to release gene drive modified organisms into the environment, research and controlled field trials should continue given the vast applications and significance of this technology. [18] The committee also suggested that gene drive research systems should have the following steps:

- Research preparation
- Laboratory-based research
- Field-based research
- Staged environmental release
- Post release surveillance

Governments should clearly define their policies and factor in public engagement and funding. Public consent in an essential component of releasing gene drives and cannot be negated. [19]

. Gene drive systems cannot be used in the public sphere without proper consent and well defined regulations and steps. Individual consent, community consent, and environmental risks need to be considered. Without individual and community consent, gene drive systems cannot be released into the wild. They will directly impact their surroundings and create an impact on the environment and hence, getting consent from the communities is essential.

8 CONCLUSION

Gene drives hold the key to solving a huge problem facing mankind today: vector borne diseases. They can have significant impact on our surroundings. With the number of deaths due to these diseases growing day by day, research on gene drives and potential applications becomes more important. More research needs to be done on gene drives along with field trials. Countless researches have shown that gene drive systems can prove to be an effective combatant against vector diseases. Public information about gene drives should also be spread in order to bring the public into the discussion and have their consent in the future. In order to increase research on gene drive system and use them in the future, clear policies should be defined by the government. Gene drives have the power to change our world in various ways and it is up to us to utilise them.

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